REMARKS

Claims 3, 4, 7, 8, 13, 18-21, 25, 26, 30, and 31 are pending in the subject application. By this Amendment, applicants have canceled claim 30 without disclaimer or prejudice, amended claims 18, 19 and 31, and added new claims 33-37. Support for the amendments may be found in the specification including *inter alia* as follows: Claim 18: page 1, lines 12-18; page 13, line 20 to page 18, line 26; Claim 19: page 1, lines 12-18; page 13, line 20 to page 18, line 26; and Claim 31: page 1, lines 12-18; page 13, line 20 to page 18, line 26. Support for new claims 33-37 may be found in the specification including *inter alia* as follows: Claim 33: page 1, lines 12-18; page 13, line 20 to page 18, line 26; page 21, line 1 to page 22, line 19; Table 1 on page 24 and Table 2 on page 25; Claim 34: page 4, lines 15-16; Claim 35: page 4, lines 15-16; Claim 36: page 17, line 6; and Claim 37: page 16, line 6 and 23. Applicants maintain that the amendments to claims 18, 19 and 31, and new claims 33-37 do not raise any issue of new matter, and request entry of this Amendment. Accordingly, claims 3, 4, 7, 8, 13, 18-21, 25, 26, 31 and 33-37 will be under examination upon entry of this Amendment.

Obviousness-Type Double Patenting Rejection

The Examiner rejected claims 3, 4, 7, 8, 13, 18-21, 25, 26, 30, and 31 on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-6 of U.S. Patent No. 6,831,073. The Examiner stated that although the conflicting claims are not identical, they are not patentably distinct from each other because the presently claimed invention is considered obvious over claims 1-6 of the '073 patent. Specifically, the Examiner stated that the instant claims differ from the reference in claiming "correcting estrogen deficiency" and "preventing osteoporosis" wherein the claims of issued patent cites "a method of treating estrogenic deficiencies" and "avoiding the appearance of osteoporosis" which are obvious. The Examiner also stated that it would have been obvious to one skilled in the art to prepare compositions useful for avoiding osteoporosis and to treat estrogenic deficiencies. The Examiner alleged that one who is familiar with the art would have been motivated to prepare

compositions of estradiol ester such as the combination of estradiol valerate and nomegesterol acetate (NOMAC) and use for the treatment of estrogen deficiencies and to avoid osteoporosis.

In response, applicants respectfully traverse the Examiner's ground of rejection, noting that claim 30 has been canceled without prejudice or disclaimer.

Claim 1 of U.S. 6,831,073 provides a method for treating estrogenic deficiencies in post menopausal women comprising continuously with interruption administering to said women a composition containing from 0.5 to 3 mg of free or esterified estradiol and 1.5 to 3.75 mg of nomegestrol acetate by daily dose.

Applicants' invention as now claimed in the subject application provides methods of (a) treating estrogen deficiencies (amended claim 18), (b) reducing bone resorption (amended claim 19) and (c) preventing growth of uterine mucosa and inducing atrophy of the endometrium without inducing a secretary transformation of the endometrium (new claim 37). As now claimed, these methods consist in continuously orally administering without interruption to menopausal women a composition containing from 0.5 to 1.5 mg of free estradiol or 1.5 to 2 mg of an estradiol ester and from 0.625 to 1.25 mg of nomegestrol acetate per daily dose. Applicants' invention as now claimed also involves a pharmaceutical composition for hormone replacement therapy (claim 31) containing from 0.5 to 1.5 mg of free estradiol or 1.5 to 2 mg of an estradiol ester and from 0.625 to 1.25 mg of nomegestrol acetate per daily dose.

Applicants note that claims 1-5 of U.S. 6,831,073 are directed to administration to post menopausal women while the present claims are directed to oral administration to menopausal women. Claim 6 of U.S. 6,831,073 recites oral administration to post menopausal women.

Applicants further note that the present invention is based on applicants' unexpected discovery that lower doses of nomegestrol acetate (0.625 to 1.25 mg) may be administered simultaneously with free estradiol (0.5 to 1.5 mg) or estradiol ester (1.5 to 2 mg) to oppose the proliferative action of the estradiol on the endometrium.

As claimed in U.S. Patent No. 6,831,073, the dose of nomegestrol acetate to be administered in combination therapy with estrogen was from 1.5 to 3.75 mg, (2.5 mg in claim 5). Applicants' now claimed invention is based on the surprising demonstration that a lower progestative dose may be used to induce endometrium atrophy with good control of bleeding.

More specifically, applicants' now claimed invention recites the following unobvious differences when compared with claims 1-6 of U.S. Patent No. 6,831,073:

	Now claimed	Claim 1 U.S. Patent No. 6,831,073
free estradiol	0.5 to 1.5 mg	0.5 to 3 mg (1.5 mg in claim 3)
estradiol ester	1.5 to 2 mg	0.5 to 3 mg (2 mg in claim 4)
nomegestrol acetate	0.625 to 1.25 mg	1.5 to 3.75 mg (2.5 mg in claim 5)
subject	menopausal women	post menopausal women
administration	oral	any route (oral in claim 6 only)

The combination of these five different features is clearly unobvious from the combination of the corresponding elements recited in any of claims 1-6 of U.S. Patent No. 6,831,073. Applicants further note that in the comparison of patented claim to pending claim required for obviousness-type double patenting, only individual claims of the patent may be considered. Thus, the claims of the patent may not be combined like prior art for this purpose. Only the specific combination of these elements as now recited provides the unexpected benefits associated with applicants' now claimed invention. Accordingly, applicants maintain that claims 3, 4, 7, 8, 13, 18-21, 25, 26, 31, as amended, and new claims 33-37 are

patentably distinct over claims 1-6 of U.S. 6,831,073, and request that this ground of rejection be withdrawn.

Rejection Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 3, 4, 7, 8, 13, 18-21, 25, 26, 30, and 31 under 35 U.S.C. 112, first paragraph, because the specification, while acknowledged as enabling for the combination of NOMAC and estradiol valerate, allegedly does not reasonably provide enablement for preventing osteoporosis and correcting estrogen deficiencies. The Examiner alleged that there is no support to show how osteoporosis can be prevented or estrogen deficiencies can be corrected in the disclosure.

In response, applicants initially note that claim 30 has been canceled without prejudice or disclaimer. Applicants have amended other claims and added new claims without conceding the correctness of the Examiner's position.

Applicants also note that amended claim 18 recites in relevant part, "method of treating estrogen deficiencies"; amended claim 19 recites in relevant part, "method of reducing bone resorption"; and new claim 33 recites in relevant part "method of preventing growth of uterine mucosa and inducing atrophy of the endometrium without inducing a secretary transformation of the endometrium." Applicants further note that on page 2 of the Office Action issued in connection with the subject application on June 18, 2002, the Examiner stated that the specification is "enabling for the method of treating estrogenic deficiencies in menopausal women." In addition, applicants maintain that "estrogen deficiency" is well-known in the art as a condition in women who lack estrogen. Applicants disagree with the Examiner's statement on page 8 of the April 19, 2006 Office Action, that "[t]here are many types of estrogen deficiencies" and that applicants "have only one example (endometrium) to support their claim for all estrogen deficiencies." Applicants maintain that the endometrium is not a type of estrogen deficiency, but is the inner membrane of the uterus in mammals. Accordingly, applicants contend that the endometrium is not a species of estrogen deficiencies as the Examiner suggests on page 8,

paragraph 3, of the April 19, 2006 Office Action. More impostantly, applicants' now claimed invention of treating estrogen deficiency by co-administration of free estradiol or estradiol ester and nomegestrol acetate in specified amounts induces endometrium atrophy and prevents bleeding. Amended claim 18 and claims dependent thereon are fully enabled by applicants' specification, including particularly Example 2 (Study of effect on nomegestrol acetate on endometrial cells) on pages 18-20, Example 3 (Study of effects of therapy on endometrium) on pages 21-22, Table 1 on page 24, and Table 2 on page 25. With respect to claim 19 as amended herein, applicants note that this claim has been amended to recite "reducing bone resorption" rather than "preventing osteoporosis." This claim and claims depended thereon are fully enabled by applicants' specification, including particularly the third paragraph on page 1. See also the prior prosecution of this application including the previously submitted Declaration Under 37 C.F.R. §1.132 of Jean-Louis Thomas, specifically Example 2 on pages 6-7 (Study of effect of combination therapy measuring bone resorption). With respect to new claim 33, this claim and claims dependent thereon are fully enabled by applicants' specification, including particularly Example 2 (Study of effect on nomegestrol acetate on endometrial cells) on pages 18-20, Example 3 (Study of effects of therapy on endometrium) on pages 21-22, Table 1 on page 24, and Table 2 on page 25.

In view of the preceding remarks, applicants maintain that claims 3, 4, 7, 8, 13, 18-21, 25, 26, 31, as amended, and new claims 33-37 are fully enabled and comply with the requirements of 35 U.S.C. §112, first paragraph, and request that the Examiner reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §103(a)

The Examiner rejected claims 3, 4, 7, 8, 13, 18-21, 25, 26, 30, and 31 under 35 U.S.C. §103(a) as allegedly obvious over Plunkett et al. in view of Blanc et al. Specifically, the Examiner asserted that Plunkett et al. teach a method of hormonal treatment for menopausal disorders involving continuous and uninterrupted administration of progestagen and estrogen. The Examiner also asserted that Blanc et al. teach continuous hormone replacement therapy combining

nomegesterol acetate and gel, patch, or oral estrogen.

In response, applicants respectfully traverse the Examiner's rejection, noting that claim 30 has been canceled without prejudice or disclaimer.

As stated above, the present invention provides methods of (a) treating estrogen deficiencies (amended claim 18), (b) reducing bone resorption (amended claim 19) and (c) preventing growth of uterine mucosa and inducing atrophy of the endometrium without inducing a secretory transformation of the endometrium (new claim 37), in menopausal women. These methods consist in continuously orally administering without interruption to menopausal women a composition containing from 0.5 to 1.5 mg of free estradiol or 1.5 to 2 mg of an estradiol ester and from 0.625 to 1.25 mg of nomegestrol acetate per daily dose. Applicants also claim a pharmaceutical composition for hormone replacement therapy (claim 31) containing from 0.5 to 1.5 mg of free estradiol or 1.5 to 2 mg of an estradiol ester and from 0.625 to 1.25 mg of nomegestrol acetate per daily dose.

Applicants maintain that Plunkett et al. in combination with Blanc et al. do not render obvious their now claimed methods or composition.

Plunkett et al. teach a dosage range for the progestative dose which spans 0.025 to 30 mg. Plunkett et al. does not specify which progestins are to be used and which dose within this large range is to be used with each type of progestins. Although, Plunkett et al. specifies certain ranges of dosage for certain progestins in Table IB, Plunkett et al. do not disclose nomegestrol acetate in applicants' claimed range as a progestin candidate for use in hormonal therapy.

Applicants maintain that Blanc et al. do not cure this deficiency. Blanc at al. teach that nomegestrol acetate may be used in combination with estrogen at a dose of 2.5 mg/day. In addition, some prior art suggests that a lower dose of prosgestin continuously administered with estrogen may not protect the endometrium. Nand et al. (Aust. NZJ Obstet. Gynaecol. (1995) volume 35, issue 1, pages

92-96) found that the progestin medroxyprogesterone acetate may be effective in protecting the endometrium at doses from 5 to 10 mg/day, but was found not to be effective at a lower dose of 2.5 mg/day. These findings were confirmed by Comerci et al. (Gynecol. Oncol. (1997) volume 64, pages 425-430) in a study of women who developed endometrial carcinoma while on combined hormone therapy with 2.5 mg/day dose of medroxyprogesterone. These findings are in contrast to applicants' work disclosed in the subject application where applicants surprisingly have demonstrated that a lower progestative dose may be used to protect the endometrium with good control of bleeding. Specifically, applicants have discovered that a specific range of free estradiol or a specific range of estradiol ester in combination with a specific low dose of nomegestrol acetate within the range 0.625 to 1.25 mg provided unexpected benefits. Applicants also maintain that this lower dosage of nomegestrol acetate is advantageous because recent studies have shown that progestins may also oppose the beneficial effects of estrogens and have suggested that higher doses of progestins may increase the risk of breast cancer. Applicants therefore maintain that the uses of specific estrogen, i.e. free estradiol or estradiol ester, and specific progestin, i.e. nomegestrol acetate, in the specific ranges now recited in the amended claims, and in new claim 33 are not obvious to those skilled in the art and provides unexpected benefits, most particularly preventing growth of uterine mucosa and inducing atrophy of the endometrium without inducing a secretary transformation of the endometrium.

In view of these remarks, applicants maintain that claims 3, 4, 7, 8, 13, 18-21, 25, 26, 31, as amended, and new claims 33-37 define unobvious subject matter and request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §103(a).

Conclusion

For the reasons set forth above, applicants maintain that the grounds for the Examiner's rejections have been overcome and respectfully request that the Examiner withdrawn these grounds of rejections and allow pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the $1,020.00 fee for the three-month extension of time and the $200 fee for one additional independent claim, is deemed necessary in connection with this Amendment. A check in the amount of $1,220.00 is enclosed. If any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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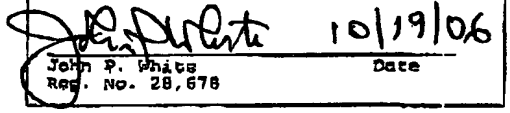

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